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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,211	11/21/2001	Timothy E. Benson	6241.N DV1	4477

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,211	BENSON, TIMOTHY E.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,21-43 and 54-61* is/are pending in the application.

4a) Of the above claim(s) *21-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 54-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/8/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-7, 21-43, and 54-61 are pending in the application.

[2] Applicants' amendment to the claims, filed July 30, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicants' amendment to the specification, filed July 30, 2004, is acknowledged.

[4] The examiner acknowledges applicants' statements regarding inventorship of the instant application. These statements are in response to the examiner's query regarding inventorship as set forth at item [4] of the Office action mailed June 30, 2004.

[5] In view of applicants' amendment to the specification, the objection to the specification as set forth at item [5] of the Office action mailed June 30, 2004 is withdrawn.

Election/Restriction

[6] Applicants' election with traverse of Group I, original claims 1-7 and newly added claims 54-61, filed July 30, 2004, is acknowledged.

[7] RESPONSE TO ARGUMENTS: Applicants traverse the restriction requirement arguing that the inventions can be "readily evaluated" in a single search without undue burden on the examiner. Applicants' argument is not found persuasive.

As stated in a previous Office action, "[e]ach of the inventions requires a separate patent and non-patent literature search requiring a different text search for each Group and thus, co-examination of the inventions of Groups I-IX would require a

serious burden on the examiner" (p.6 of the Office action mailed June 30, 2004). Each of inventions I-IX recite different limitations requiring a different text-based, and in the case of Group I, a different sequence-based search. As applicants have provided no evidence or line of reasoning as to why the inventions of Groups I-IX would not require a separate search, the restriction is deemed proper.

[8] Claims 21-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on July 30, 2004.

[9] Claims 1-7 and 54-61 are being examined on the merits.

Priority

[10] Applicant's claim to domestic priority under 35 USC § 121 to US non-provisional application 09/632,947, filed August 04, 2000, now US Patent 6,356,845, is acknowledged. Applicants' claim to domestic priority under 35 USC § 119(e) to provisional application number 60/147,164, filed August 04, 1999, is acknowledged.

Information Disclosure Statement

[11] All references cited in the information disclosure statement (IDS) filed April 08, 2002 have been considered by the examiner. A copy of the IDS is attached to the instant Office action.

Drawings

[12] The drawings are objected to as the first sheet of Figures 4 and 12 (see Appendices A and B) do not correspond to the descriptions of Figures 4 and 12 in the specification (pages 10 and 12, respectively). Appropriate correction is required.

Specification/Informalities

[13] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification, *e.g.,* page 32, line 20 and all other hyperlinks embedded in the specification, is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[14] Claim(s) 1-6 and 51-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1-6, 55-57, and 59-61 are indefinite in the recitation of "amino acids listed in Table..." Without a reference amino acid sequence, *e.g.,* SEQ ID NO:1, it is unclear

as to the amino acids and their relative positions in the molecule, molecular complex, or protein. It is suggested that applicants clarify the meaning of the claims.

[b] Claim 7 is indefinite in the recitation of "structurally homologous to an *S. aureus* MurB molecule or molecular complex" as it is unclear as to whether the recited "structure" is intended to be interpreted as the primary amino acid sequence or the three-dimensional structure. Further, it is unclear as to how "homologous" a molecule or molecular complex must be to be included within the scope of the claim. Also, it is unclear as to the proteins that are considered to be *S. aureus* MurB molecules or molecular complexes such that a skilled artisan can determine whether the claimed molecule or molecular complex is sufficiently "structurally homologous" to be included within the scope of the claim. It is suggested that applicants clarify the meaning of the term.

[c] Claim 7 is indefinite in the recitation of "represented by" as it is unclear as to the intended meaning of the term in the context of a molecule or molecular complex. It is suggested that applicants clarify the meaning of the term.

[d] Claims 55-57 and 59-61 are confusing in that the protein of claim 54 or 58 is not limited to having the amino acids listed in Tables 1-6. Claims 54 and 58 are drawn to polypeptides consisting of a portion of the amino acid sequences listed in the claims. Neither the specification nor the claims provide a definition for the term "polypeptide" and it is unclear as to the minimum number of amino acids that are required for a "portion of *S. aureus* MurB" to be considered a "polypeptide." In accordance with MPEP

2111, claims 54 and 58 can be interpreted as a peptide with as few as two amino acids. It is suggested that applicants clarify the meaning of the claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[15] Claim(s) 1-7 and 54-61 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim(s) are drawn to a molecule or molecular complex. The claim(s) read on a product of nature and should be amended to indicate the hand of the inventor, e.g., by insertion of "purified" or "isolated". See MPEP § 2105.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[16] Claim(s) 54-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 54 (claims 55-57 dependent therefrom) and 58 (claims 59-61 dependent therefrom) are drawn to a polypeptide consisting an amino acid starting at position 37 to 42 and ending at position 310 to 312 of SEQ ID NO:1 (claim 54) or a polypeptide consisting an amino acid starting at position 42 to 155 and ending at position 274 to 309 of SEQ ID NO:1 (claim 58). Applicants assert support can be found for these claims at pages 4-6 of the specification. However, the examiner can find no support for a polypeptide consisting of a range of amino acids starting at position 37 to 42 and ending at position 310 to 312 of SEQ ID NO:1 or a polypeptide consisting of a range of amino acids starting at position 42 to 155 and ending at position 274 to 309 of SEQ ID NO:1 in the specification, claims, or drawings as originally filed. In this case, applicants' cited support lists various (noncontiguous) amino acids that are involved in ligand binding and does not provide support for a polypeptide consisting of a range of amino acids starting at position 37 to 42 and ending at position 310 to 312 of SEQ ID NO:1 or a polypeptide consisting of a range of amino acids starting at position 42 to 155 and ending at position 274 to 309 of SEQ ID NO:1. Applicants are invited to direct the examiner's attention to supporting disclosure for the limitations recited in claims 54 and 58.

[17] Claim(s) 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-7 are drawn to

a genus of molecules or molecular complexes comprising at least a portion of an *S. aureus* MurB or MurB-like FAD binding pocket or substrate binding pocket or molecules or molecular complexes that are homologous thereto.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the claimed molecules or molecular complexes, *i.e.,* the *S. aureus* MurB of SEQ ID NO:1. The specification fails to describe any additional representative species of the recited genus of molecules or molecular complexes as encompassed by the claims. In this case, the single representative species fails to describe the genus of molecules or molecular complexes, which encompasses *widely* variant species with respect to the structures and functions of the molecules or molecular complexes. Given the lack of description of a representative number of

species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[18] Claims 1-7 and 54-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *S. aureus* MurB polypeptide of SEQ ID NO:1, does not reasonably provide enablement for all molecules or molecular complexes as encompassed by claims 1-7 and 54-61. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: Claims 1-7 are so broad as to encompass all molecules or molecular complexes comprising at least a portion of an *S. aureus* MurB or MurB-like FAD binding pocket or substrate binding pocket as encompassed by

claims 1-7. The claims broadly encompass any protein. Claims 54-61 broadly encompass fragments of SEQ ID NO:1, including fragments of as few as two amino acids. In this case the disclosure is limited to the *S. aureus* MurB polypeptide of SEQ ID NO:1.

- The lack of guidance and working examples: The specification provides only a single working example of the claimed molecule, molecular complex, or polypeptide, *i.e.,* the *S. aureus* MurB polypeptide of SEQ ID NO:1. Regarding claims 1-7, the specification fails to provide guidance regarding those amino acids of SEQ ID NO:1 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired MurB activity. Furthermore, the specification fails to provide guidance as to how to use those variant polypeptides having activities other than the desired MurB activity, *e.g.,* non-functional polypeptides or polypeptides having activity other than MurB activity. Regarding claims 54-61, the specification fails to teach how to use all claimed fragments of SEQ ID NO:1 as encompassed by the claims, including those fragments that are too small to generate antibodies to SEQ ID NO:1.

- The high degree of unpredictability in the art is supported by the state of the art: The amino acid sequence of a protein determines its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired MurB activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired MurB activity/utility are limited and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions.

- The state of the art provides evidence for the high degree of unpredictability in altering a protein's sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The teachings of Branden et al. are exemplified by Witkowski et al. (*Biochemistry* 38:11643-11650), who teach that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

- The amount of experimentation required is undue: While methods of generating variants of a given protein are known in the art, *e.g.,* site-directed mutagenesis, it is not routine in the art to screen for *all* proteins having a substantial number of substitutions or modifications and having *any* function, as encompassed by the instant claims. Further, it is not routine in the art to experiment to find utilities for all fragments of a polypeptide as encompassed by the claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high degree of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all molecules or molecular complexes as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

[19] Claim(s) 1-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Wallis et al. (US Patent 6,225,098 B1). Claims 1-7 are drawn to a molecule or molecular complex comprising at least a portion of an *S. aureus* MurB or MurB-like FAD binding pocket or substrate binding pocket as encompassed by the claims. Wallis et al. teach an *S. aureus* MurB polypeptide (see particularly SEQ ID NO:2 and 3). This anticipates claims 1-7 as written.

[20] Claim(s) 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Database GenBank Accession Number P08373. Claims 1-7 are drawn to a molecule or molecular complex as described above. Database GenBank Accession Number P08373 teaches an *E. coli* MurB polypeptide. This anticipates claims 1-7 as written.

[21] Claim(s) 54-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Sigma Chemical Catalog 1993. Claims 54 and 58 are drawn to a polypeptide consisting of a portion of amino acids starting at position 37 to 42 and ending at position 310 to

312 of SEQ ID NO:1 or amino acids starting at position 42 to 155 and ending at position 274 to 309 of SEQ ID NO:1. Claims 55-57 and 59-61 limit the three-dimensional configuration of the amino acids. As stated above, the term "polypeptide" has not been defined in the specification or the claims and has been broadly interpreted as a peptide of as few as two amino acids. Sigma Chemical Catalog 1993 teaches a Tyr-Arg peptide (p. 1067), which is a portion of amino acids starting at position 37 to 42 and ending at position 310 to 312 of SEQ ID NO:1 or amino acids starting at position 42 to 155 and ending at position 274 to 309 of SEQ ID NO:1, *i.e.,* amino acids 187-188 of SEQ ID NO:1. This anticipates claims 54-61 as written.

[22] It is noted that Sigma Chemical Catalog 1993 does not teach the three-dimensional configuration of the Tyr-Arg peptide. However, since the Office does not have the facilities for examining and comparing applicants' polypeptide with the polypeptide of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (*i.e.,* that the polypeptide of the prior art does not possess the same material structural and functional characteristics of the claimed polypeptide). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Conclusion

[23] Status of the claims:

- Claims 1-7, 21-43, and 54-61 are pending.
- Claims 21-43 are withdrawn from further consideration.

- Claims 1-7 and 54-61 are rejected.

- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 6:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1652
09-28-04